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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/699,003	10/26/2000	M. Rigdon Lentz	LEN 101 CIP CON	7721

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EXAMINER	
BIANCO, PATRICIA	
ART UNIT	**PAPER NUMBER**
3762	

DATE MAILED: 12/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/699,003	LENTZ, M. RIGDON	
	Examiner	Art Unit	
	Patricia M Bianco	3762	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-10,12 and 16-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-10,12 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*.

DETAILED ACTION

Response to Amendment

1. Applicant's amendment filed on October 4th, 2004 has been entered. Claims 1, 8, 12 & 20 have been amended. Claims 1-6, 8-10, 12, and 16-20 are currently pending.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. newly amended claim 1 now requires that the reduction in amount of transformed, infected, or diseased tissue is reduced "as compared to the amount prior to initiation of treatment" in lines 4-5. There is no support for this language in the originally filed specification.

Specification

3. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: newly amended claim 1 now requires that the reduction in amount of transformed, infected, or diseased tissue is reduced "as compared to the

amount prior to initiation of treatment" in lines 4-5. There is no support for this language in the originally filed specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-4, 8, 12, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lentz (4,708,713) in view of Selinsky et al. ("*Multifaceted inhibition of anti-tumor immune mechanism by soluble tumour necrosis factor receptor type I*").

Lentz discloses a method and system for inducing an immune response against diseases and conditions that result from or are dependent upon deficiencies in the immune response system. Lentz teaches that immunosuppressive components are removed from the body until the level of immunosuppressive components in the body are reduced to a level which cause an acute immune response against the disease or condition. Such diseases or conditions can be cancer or neoplastic tissue (i.e. a tumor). Lentz discloses that after treatment with the disclosed invention, the tumor hemorrhages, lymphocytic infiltration occurs and the tumor liquefies. This is an immunological attack of the tumor, resulting in tumor necrosis, and this is an indication of acute immune response. (Col. 2, line 64-col. 3, line16 and examples). The system

includes a filter, inlet and outlet means for connection to a pump, tubing for fluid delivery and return, and a syringe pump (col. 3, lines 56-68). Lentz's method comprises withdrawing blood from a patient, extracorporeally treating the blood to selectively separate the components having a low molecular weight, and returning the treated blood to the patient, which will inherently initiate an immune response against the disease or condition the patient is suffering from. The blood is treated by passing through a filter that removes the immunosuppressive components from the blood. Lentz also discloses that the treatment is carried out on multiple occasions. With respect to claim 3, it would have been obvious to perform the method on one blood volume since that would not affect the patient in an adverse manner. With respect to claim 4, it would have been obvious to one in the art that the method of Lentz for inducing immune response against the diseased tissue (i.e. tumor) would be performed in multiple treatments, since it is highly unlikely that one treatment would completely eradicate the tumor. With respect to claim 20, the recitation of "wherein the blood is plasma" has not been given patentable weight because it is narrative in form. In order to be given patentable weight, a functional recitation must be expressed as "means" for performing the specified function, as set forth in 35 USC § 112, 6th paragraph, and must be supported by recitation in the claim of sufficient structure to warrant the presence of the functional language (In re Fuller). Therefore, the tubing in the system of Lentz is clearly capable of circulating plasma through the tubing. With respect to claim 5, the method and system of Lentz including treating the tissue multiple therapies in methods of treating cancer was well known in the art at the time of the invention. As shown in the

figures, necessary fluids may be added from bottle (31) to the blood. Lentz also teaches that plasma may be treaded in accordance with the inventive method and system to remove immunosuppressive components.

Selinsky et al. ("*Multifaceted inhibition of anti-tumor immune mechanism by soluble tumour necrosis factor receptor type I*") teaches of a procedure to remove soluble tumor necrosis factor receptor type I (TNFR1), which is a biological component that inhibits or blocks immunological mechanisms in tumor cell eradication, by ultrapheresis as a treatment for cancer immunotherapy. The removal of TNFR1 allows tumor necrosis factor (TNF), which induces cell death (apoptosis), to circulate in the body and destroy the tumor cells.

Lentz teaches of the removal of "immunosuppressive components" from the blood of a patient. The TNFR1 is seen to be equivalent to said component since it suppresses a natural immunological component, TNF, from performing its function. At the time of the invention, it would have been obvious to one having skill in the art to modify the method of Lentz to select TNFR1 as the soluble cytokine receptor molecule to be removed in order to enhance the death of tumor cells in cancer patients and improve the patient's own immune response against the tumor.

5. Claims 9, 10 and 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lentz & Selinsky in view of Okarma et al. (5,523,096). Lentz & Selinsky discloses the invention substantially as claimed, see rejection supra. Lentz & Selinsky, however, fails to disclose specifically the device being an absorbent column

for removing cytokines or TNF from the blood wherein the column has immobilized cytokine fragments through which blood is passed. Okarma et al. discloses an extracorporeal system for removing cytokines from the blood, such as TNF, using an absorption matrix in a column (see col. 3, 3ine 28-col. 4, line 14 & fig. 1B). At the time of the invention, it would have been obvious to combine Lenz and Okarma by substituting the absorbent column of Okarma for the device of Lentz since the removal of cytokines using said column performs an equivalent function, that of removing components from blood. Further, Okarma teaches that the removal of cytokines is done to control the immune system's response to diseases and provide lower circulating levels of cytokines in the blood of a patient.

6. Claims 5 & 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lentz ('713) and Selinsky in further view of Feinman et al. (*Tumor Necrosis Factor Is An Important Mediator of Tumor Cell Killing By Human Monocytes).* Lentz & Selinsky substantially disclose the invention as claimed, see rejection supra. Lentz & Selinsky, however, fail to disclose specifically the further treatment with an agent selected from the group consisting of anti-angiogenic compounds, procoagulant compounds, cytokines, chemotherapeutic agents, and radiation in dosage formulation, or wherein the agent is a cytokine selected from the group of GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF.

Feinman et al. discloses the use of interferon-γ to increase monocyte cytotoxicity by sensitizing target cells to the lytic action of TNF (see abstract). Therefore, at the time

of the invention, it would have been obvious to one having ordinary skill in the art to modify the methods of Lentz and Selinsky to include administering interferon-γ with a reasonable expectation of success, because Feinman has disclosed that interferon-γ (a cytokine that is known in the art to be highly immunoregulatory) will increases monocyte cytotoxicity by sensitizing target cells to the lytic action of TNF. Thus, the combination of removing soluble TNF receptor and sensitizing target cells to the lytic action of TNF by interferon-γ will enhance the therapeutic potential and assist the body in maintaining a fully functional immune system. With respect to the cytokine being from the group of GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF, it would have been obvious to one having ordinary skill in the art to chose any of the group instead of interferon-γ if desired, since it has been held to be within the general skill of a worker in the art, such as the physician in charge of the patient's care, to select a known agent or compound on the basis of its suitability for the treatment being performed. *In re Leshin*, 125 USPQ 416.

7. Claims 1-4, 8-10, 12, and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Selinsky et al. ("*Multifaceted inhibition of anti-tumor immune mechanism by soluble tumour necrosis factor receptor type I*") and Van Zee et al. (*Tumor necrosis factor soluble receptors circulate during experimental and clinical inflammation and can protect against excessive tumor necrosis factor α in vitro and in vivo)* in view of Lentz ('713) and Maraskovsky et al. (6,017,527).

Selinsky teaches antibodies that are specific for sTNFR-I and the use of Ultrapheresis, well known to selectively remove components within a defined molecular range, for treating cancer. sTNFR-I is a potent inhibitor of TNF with the potential to suppress a variety of effector mechanisms important in tumor immunity (see abstract). Selinsky also teaches that soluble TNFR-I is removed by Ultrapheresis (pg. 88) and sTNFR-I effectively inhibits immune response *in vivo* and demonstrates that its modulation is a legitimate therapeutic avenue (pg. 92). It also describes an anti-human sTNFR-I antibody. Selinsky also indicates that "We therefore, propose the development of methods and/or reagents capable of specifically removing sTNFR-I, or antagonizing its effects *in situ*, as unconventional, yet promising, strategies for cancer immunotherapy" (pg. 92). Van Zee discloses antibodies for both the sTNFR-I and sTNFR-II receptors (see abstract and pg. 4846).

Selinsky and Van Zee do not teach of the removal of blood for treatment against the diseased tissue in the blood and the subsequent return of treated blood to the patient after removal of cytokine receptor molecules. Selinsky and Van Zee also do not teach the removal of immunosuppressive components using an immobilized antibody for binding the molecules, wherein the bound antibody is immobilized in a column.

As discussed above, Lentz teaches of a method and system for inducing an immune response by removing immunosuppressive components from the blood that has been removed from a patient and returning the treated blood to the patient. See rejection supra for further details on Lentz.

Maraskovsky teaches of a method of stimulating an immune response in a patient providing a method in which antibodies specific to antigens are immobilized onto a surface such as beads in a column (col. 4, lines 13-25). The antibodies remove specific cells.

At the time of the invention, it would have been obvious to one having ordinary skill in the art to use the method of Selinsky to remove cytokine receptors using antibodies to the cytokine receptors (TNFR-I and TNFR-II, see above Selinsky and Van Zee) that inhibit immune response as taught by Lentz for removing diseased tissue in the treatment of cancer from the blood of a patient with a column of immobilized antibodies for removing the soluble cytokine receptors as taught by Maraskovsky. In addition, one of ordinary skill in the art would have been motivated, with a reasonable expectation of success, to combine Selinsky, Van Zee, Lentz and Maraskovsky because Selinsky also indicates that "We therefore, propose the development of methods and/or reagents capable of specifically removing sTNFR-I, or antagonizing its effects *in situ*, as unconventional, yet promising, strategies for cancer immunotherapy" (pg. 92) Moreover, one of ordinary skill in the art would have been motivated, with a reasonable expectation of success, to combine the teachings of Selinsky, Lentz and Maraskovsky because Maraskovsky teaches antibodies immobilized on beads for removal of antigens from blood. Thus, it would have been obvious to use the method of Maraskovsky to immobilize an antibody of Selinsky or Van Zee which specifically binds the sTNFR-I or sTNFR-II, wherein the sTNFR-I or sTNFR-II inhibits the immune

response, and is removed using the device in the method taught by Lentz using an immobilized antibody.

8. Claims 5 & 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Selinsky et al. ("*Multifaceted inhibition of anti-tumor immune mechanism by soluble tumour necrosis factor receptor type I*") and Van Zee et al. (*Tumor necrosis factor soluble receptors circulate during experimental and clinical inflammation and can protect against excessive tumor necrosis factor α in vitro and in vivo)* in view of Lentz ('713) and Maraskovsky et al. ('527) in further view of Feinman et al. (*Tumor Necrosis Factor Is An Important Mediator of Tumor Cell Killing By Human Monocytes).* Selinsky, Van Zee, Lentz, & Maraskovsky substantially disclose the invention as claimed, see rejection supra. Selinsky, Van Zee, Lentz, & Maraskovsky, however, fail to disclose specifically the further treatment with an agent selected from the group consisting of anti-angiogenic compounds, procoagulant compounds, cytokines, chemotherapeutic agents, and radiation in dosage formulation, or wherein the agent is a cytokine selected from the group of GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF.

Feinman et al. discloses the use of interferon-γ to increase monocyte cytotoxicity by sensitizing target cells to the lytic action of TNF (see abstract). Therefore, at the time of the invention, it would have been obvious to one having ordinary skill in the art to modify the methods of Selinsky, Van Zee, Lentz, & Maraskovsky to include administering interferon-γ with a reasonable expectation of success, because Feinman has disclosed that interferon-γ (a cytokine that is known in the art to be highly

immunoregulatory) will increases monocyte cytotoxicity by sensitizing target cells to the lytic action of TNF. Thus, the combination of removing soluble TNF receptor and sensitizing target cells to the lytic action of TNF by interferon-γ will enhance the therapeutic potential and assist the body in maintaining a fully functional immune system. With respect to the cytokine being from the group of GM-CSF, erythropoietin, thrombopoetin, G-CSF, M-CSF and SCF, it would have been obvious to one having ordinary skill in the art to chose any of the group instead of interferon-γ if desired, since it has been held to be within the general skill of a worker in the art, such as the physician in charge of the patient's care, to select a known agent or compound on the basis of its suitability for the treatment being performed. *In re Leshin*, 125 USPQ 416.

Terminal Disclaimer

9. The terminal disclaimer filed on October 26th, 2004 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patents 6,231,563, 6,620,382, and U.S.S.N. 09/709,045 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Information Disclosure Statement

10. Applicant alleges that an IDS filed October 2nd, 2003 (paper no. 8) was not considered. The examiner has already considered this IDS and has previously mailed the intitalled PTO-forms 1449 as an attachment to the Office Action mailed February 9th, 2004 (paper no. 13). However, copies have been attached to this action as well.

Response to Arguments

11. Applicant's arguments filed October 4th, 2004 have been fully considered but they are not persuasive. With respect to the rejections under 35 U.S.C. 103, applicant argues that the rejections cannot be responded to since no citation nor copy of the references were provided. However, the examiner would like to point out that they were not supplied, nor need by supplied by the examiner, with the last office action because all were supplied by the examiner with an earlier office action or by applicant in an IDS.

Please note: on page 5 of the response, applicant alleges that claims 20-23 were rejected under 35 U.S.C. 112, however, claims 21-23 are not pending in the application; also, no signed copy of the Declaration has been received and therefore it has not been considered at this time. It will be considered upon receipt of an executed copy.

Conclusion

12. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia M Bianco whose telephone number is (571) 272-4940. The examiner can normally be reached on Monday to Friday 9:00-6:30, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Angela Sykes can be reached on (571) 272-4955. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

December 21st, 2004

Patricia M Bianco
Primary Examiner
Art Unit 3762

PATRICIA BIANCO
PRIMARY EXAMINER